Phase II, Multicenter, Single-Arm, Feasibility Study of Eribulin Combined With Capecitabine for Adjuvant Treatment in Estrogen Receptor-Positive, Early-Stage Breast Cancer

John W. Smith II,[1] Svetislava Vukelja,[2] Anthony D. Hoffman,[3] Vicky E. Jones,[4] Kristi McIntyre,[5] Erhan Berrak,[6] James X. Song,[6] Joyce O'Shaughnessy[7]

Abstract

Eribulin plus capecitabine as adjuvant therapy was feasible in postmenopausal women with early-stage, human epidermal growth factor receptor 2-negative, estrogen receptor-positive breast cancer. The mean relative dose intensity was 90.6%, and the feasibility rate was 81.3% with the standard dosing schedule for both drugs. An alternative schedule for capecitabine (7 days on, 7 days off) was better tolerated in a supplemental group of 10 patients.

Background: The present phase II, open-label, multicenter study explored the feasibility, safety, and tolerability of eribulin, a novel non-taxane microtubule inhibitor, plus capecitabine as adjuvant therapy. **Patients and Methods:** Postmenopausal women with early-stage, human epidermal growth factor receptor 2 (HER2)-negative, estrogen-receptor (ER)-positive breast cancer received four 21-day cycles of treatment with eribulin mesylate (1.4 mg/m^2 intravenously on days 1 and 8 of each cycle) combined with capecitabine (900 mg/m^2 orally twice daily on days 1-14 of each cycle [standard schedule] or 1500 mg orally twice daily using a 7-days on/7-days off schedule [weekly schedule]). Feasibility was determined by the relative dose intensity (RDI) of the combination using prespecified criteria for 80% of patients achieving an RDI of $\geq$ 85%, with a lower 95% confidence boundary $>$ 70%. **Results:** The mean RDI was 90.6%, and the feasibility rate was 81.3% among women (n = 67, mean age, 61.3 years) receiving the standard schedule and 95.6% and 100% among women (n = 10, mean age 62.3 years) receiving the weekly schedule. Dose reductions, missed doses, and withdrawals due to adverse events (most commonly hand-foot syndrome) ascribed to capecitabine led to a higher RDI (93.5% vs. 87.8%) and feasibility rate (82.8% vs. 71.9%) for eribulin than for capecitabine using the standard dosing schedule. The most common adverse events were alopecia and fatigue. **Conclusion:** Eribulin plus capecitabine with standard or weekly dosing schedules is feasible in patients with early-stage, HER2-negative, ER-positive breast cancer. Full-dose eribulin (1.4 mg/m^2 on days 1 and 8) with capecitabine (1500 mg orally twice daily, 7 days on/7 days off) is recommended as a regimen for further evaluation.

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Introduction

Standard adjuvant chemotherapy for early-stage human epidermal growth factor receptor-2 (HER2)-negative breast cancer is effective but has been associated with cumulative and overlapping toxicities, such as myelosuppression and gastrointestinal events, among others, that can limit the therapeutic utility of current drug combinations.[1,2] Therefore, new drug combinations that are better tolerated and will improve outcomes are needed. One possibility is

[1]Compass Oncology, The US Oncology Network, Portland, OR
[2]Texas Oncology-Tyler, The US Oncology Network, Tyler, TX
[3]Eastchester Center for Cancer Care, Bronx, NY
[4]Yakima Valley Memorial Hospital-North Star Lodge Cancer Center, Yakima, WA
[5]Texas Oncology-Dallas Presbyterian Hospital, The US Oncology Network, Dallas, TX
[6]Eisai Inc., Woodcliff Lake, NJ
[7]Texas Oncology-Baylor Charles A. Sammons Cancer Center, The US Oncology Network, Dallas, TX

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Address for correspondence: John W. Smith II, MD, Compass Oncology, The US Oncology Network, 5050 NE Hoyt St, Suite 256, Portland, OR 97213-2996
E-mail contact: john.smith@usoncology.com

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to optimize combination chemotherapy regimens by the addition of new, promising cytotoxic agents.

Eribulin mesylate is a novel non-taxane microtubule inhibitor that induces mitotic arrest and apoptosis in cancer cells by mechanistically distinct effects on microtubule dynamics that are not shared by other known anticancer tubulin-targeted agents.[2-5] It has been approved by the US Food and Drug Administration for the treatment of patients with metastatic breast cancer who have previously received $\geq$ 2 chemotherapeutic regimens (including an anthracycline and a taxane in either the adjuvant or metastatic setting).[6] Eribulin has shown efficacy in patients with extensively pretreated locally advanced or metastatic breast cancer. The objective response rate in a phase III clinical study was significantly greater for patients treated with eribulin than for those receiving treatment of physician's choice (12% vs. 5%; $P = .002$), accompanied by an increase in overall survival (hazard ratio, 0.81; 95% confidence interval [CI], 0.66-0.99; $P = .04$).[2,7] Eribulin has also shown a predictable side effect profile, with the most common adverse events (AEs) associated with treatment generally neutropenia, fatigue, alopecia, nausea, and anemia.[2,7,8]

The focus of the present study was to explore the feasibility of adding eribulin to capecitabine as adjuvant therapy in patients with early-stage, estrogen receptor (ER)-positive breast cancer. Capecitabine was previously studied in the adjuvant setting versus standard chemotherapy in postmenopausal women > 65 years old and in the ER-positive subset.[9] No difference was seen in the outcomes.[9] Eribulin and capecitabine have key toxicities that do not overlap; thus, theoretically, the eribulin plus capecitabine combination could improve the probability that the regimen will be well tolerated and more efficacious. Preliminary safety data from a phase II study of the combination and efficacy data indicating considerable activity in metastatic breast cancer patients also provided justification for the initiation of this pilot adjuvant study.[10]

Patients and Methods

The present study was conducted at 20 centers in The US Oncology Network after approval of the protocol by the central US Oncology investigational review board. Each patient voluntarily provided written informed consent before study participation, and the patients were free to discontinue at any time. The present study was conducted in accordance with the principles of the World Medical Association Declaration of Helsinki, 2008, the International Conference on Harmonization Guideline for Good Clinical Practice, and applicable national and local laws and regulations.

Patients

Eligible patients included postmenopausal women with histologically confirmed early-stage (stage I-II), HER2-negative, ER-positive breast cancer. Patients also must have had adequate liver, renal, and bone marrow function, had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, and been eligible for adjuvant therapy to begin within 84 days of the final surgical procedure for breast cancer.

The exclusion criteria included stage III and IV invasive breast cancer; any nonmalignant systemic disease that would preclude the use of any of the study therapy drugs, including current gastrointestinal disease or other conditions resulting in an inability to take or absorb oral medications; and pre-existing neuropathy (grade > 2). Premenopausal women were not eligible because of the absence of cyclophosphamide, which has ovarian function suppressive effects.

Study Design

The present study was a single-arm, open-label, phase II feasibility study conducted from August 2011 to April 2014. The study treatment phase included four 21-day cycles of treatment (eribulin combined with capecitabine). Protocol eligibility was confirmed, and hematology, clinical chemistry, vital signs, and ECOG PS assessments and physical examinations were conducted within 2 weeks before the start of study treatment. Also, a baseline 12-lead electrocardiogram (ECG) was performed within 3 days of the first day of the first treatment cycle.

Eligible patients were treated with eribulin mesylate 1.4 mg/m^2 administered intravenously over 2 to 5 minutes on days 1 and 8 of each 21-day cycle. Eribulin was given in combination with capecitabine, which was administered using 1 of 2 different dosage regimens. In the first regimen, used for most patients (n = 67), 900 mg/m^2 capecitabine was administered orally twice daily (a total of 1800 mg/m^2) on days 1 through 14 of each 21-day cycle. The second dosing regimen for capecitabine was initiated after dose reductions and treatment discontinuations were noted and attributed to capecitabine-related toxicities, including grade 3 or 4 gastrointestinal events and hand-foot syndrome, such that the feasibility of administering $\geq$ 85% of the planned capecitabine dose was 71.9%. Thus, capecitabine was administered to an additional cohort of 10 patients at a fixed dose of 1500 mg given orally twice daily on a 7-days on/7-days off schedule continuously during the 4 cycles. This regimen for capecitabine was based on mathematical modeling[11] and has been shown to have an acceptable toxicity profile, including minimal gastrointestinal toxicity, when given in combination with bevacizumab to patients with metastatic breast cancer.[12] Eribulin was administered at the study site, ensuring compliance with eribulin dosing. The patients recorded in a daily diary the number of tablets of capecitabine taken.

Toxicities were managed in individual patients by treatment interruptions and subsequent dose reductions of eribulin or capecitabine, or both. A maximum of 2 dose reductions of either drug was allowed. Treatment could be delayed in the event of grade 3 or 4 toxicities resulting from either agent. If relationship to a specific study drug could be ascertained, the dosage of only that study drug was modified.

Warfarin was not permitted because of the likelihood of drug−drug interactions between capecitabine and warfarin-derived anticoagulant therapy. Granulocyte colony-stimulating factor (filgrastim only) could be used in cycles 2, 3, and 4 if the patient required a treatment delay of a new cycle owing to an episode of neutropenia; pegfilgrastim was not allowed.

The evaluations included hematology and clinical chemistry assessments, vital signs, and physical examinations, which were performed before study treatment administration on day 1 of each treatment cycle. The hematology assessments and vital signs were also performed before treatment on day 8 of each treatment cycle. An ECG was performed on days 1 and 8 of cycle 1 only (before dosing and immediately after eribulin administration). AEs and concomitant medications were assessed throughout the study. The

end-of-treatment visit occurred within 30 days after the last dose of study medication and included physical examination, recording of vital signs, ECG, ECOG PS, hematology and clinical chemistry assessments, and reports of concomitant medications and AEs.

Statistical Analysis

The primary endpoint of the present study was the feasibility of administering adjuvant eribulin combined with capecitabine for 4 cycles of treatment. Feasibility analyses were conducted on the evaluable patient data set, which included patients who had met all inclusion and exclusion criteria, had received $\geq$ 1 dose of eribulin plus capecitabine, and had completed the study or discontinued prematurely because of AEs or disease progression. The sample size of the first cohort was based on a minimum of 57 evaluable patients, which would discriminate between true feasibility rates of $\leq$ 70% and $\geq$ 85% at a type I error of 5% and power of $\geq$ 85%. The null hypothesis (H_0) was defined as feasibility $\leq$ 70%.

For each patient, the regimen was considered feasible if that patient was able to achieve a relative dose intensity (RDI) of $\geq$ 85% of the 4 cycles of eribulin plus capecitabine. The overall RDI for each patient was calculated as (Dea/Dep + Dca/Dcp)/2, where Dep is the planned dose of eribulin (determined by the patient's body surface area), Dea is the actual total dose of eribulin administered during the full 4-cycle regimen, Dcp is the planned dose of capecitabine, and Dca is the actual delivered dose of capecitabine during the full 4-cycle regimen.

The combination regimen was considered feasible and would warrant further clinical study if $\geq$ 80% of evaluable patients were able to achieve an RDI of $\geq$ 85%. A 95% CI was constructed using the exact method. The observed study feasibility rate in the first cohort was also compared to a feasibility rate of 70% using a 1-sample binomial test. Exploratory feasibility analyses were also performed for patients who were and were not receiving growth factors. Descriptive statistics were used to summarize the feasibility data in the second cohort.

The evaluation of safety (extent of exposure, AEs, clinical laboratory results, vital signs, ECG findings, ECOG PS, and physical examination findings) was performed on the safety analysis set, which included all patients who had received $\geq$ 1 dose of study treatment and had undergone $\geq$ 1 post-baseline safety assessment.

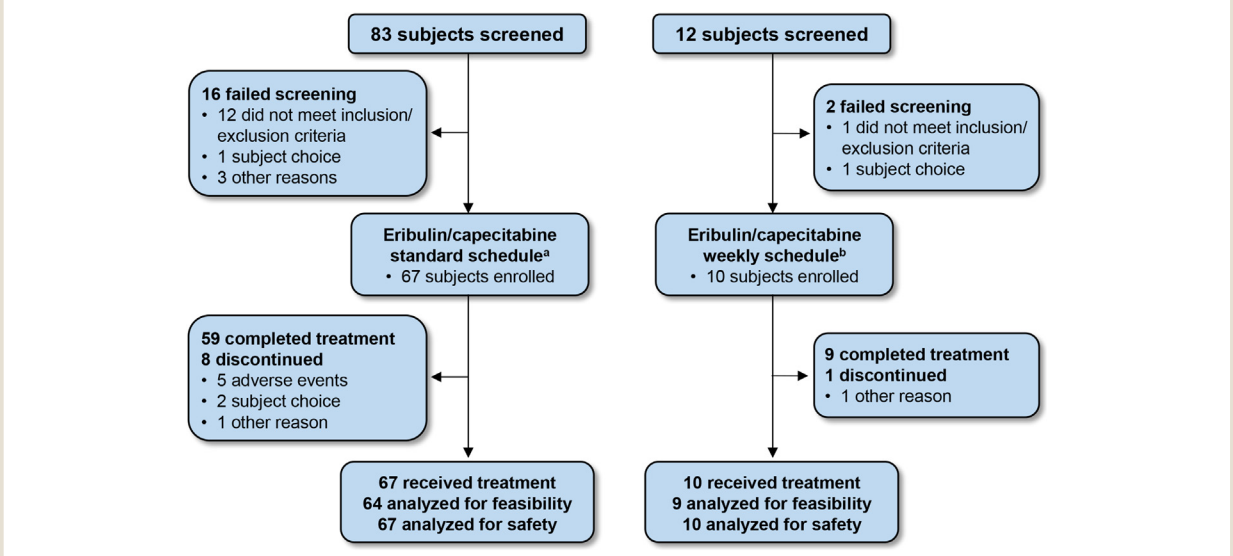
The demographic data and other baseline characteristics were summarized for the safety analysis set, which included all patients who had received $\geq$ 1 dose of eribulin plus capecitabine, using descriptive statistics. Analyses of efficacy and safety data were performed separately in each cohort.

Results

Study Patients

A total of 83 patients were screened, and 67 received the standard dosing schedule (eribulin mesylate 1.4 mg/m^2 on days 1 and 8 of each 21-day cycle plus capecitabine 900 mg/m^2 twice daily on days 1-14 of each 21-day cycle). An additional 12 patients were screened, and 10 were treated with the weekly dosing schedule (eribulin mesylate 1.4 mg/m^2 on days 1 and 8 of each 21-day cycle plus capecitabine 1500 mg twice daily on a 7-days on/7-days off schedule throughout the 4 cycles). Most patients not enrolled after screening were excluded because of failure to meet the inclusion and/or exclusion criteria (Figure 1). A total of 8 patients (12%) did not complete the 4 cycles of treatment. Three patients receiving the standard dosing schedule discontinued (2 withdrew early because of administrative reasons and 1 withdrew because of anxiety and depression not related to the study treatment), leaving 64 patients evaluable for feasibility analyses. An additional 5 patients did not complete 4 cycles of treatment because of AEs (neutropenia in 2

Figure 1 Distribution of Study Patients [a]Eribulin mesylate 1.4 mg/m^2 on days 1 and 8 plus capecitabine 900 mg/m^2 twice daily on days 1 through 14 on a 21-day cycle. [b]Eribulin mesylate 1.4 mg/m^2 on days 1 and 8 on a 21-day cycle plus capecitabine 1500 mg twice daily on a 7-days On/7-Days off schedule for 4 cycles



patients and gastritis, peripheral neuropathy, and muscle weakness occurring in 1 patient each). One patient receiving the weekly capecitabine schedule discontinued (for a reason other than progressive disease, AEs, administrative, or lost to follow-up), leaving 9 patients evaluable for feasibility analyses in this cohort. All enrolled patients receiving the standard and weekly dosage schedules were included in the safety analysis sets (Figure 1).

The baseline characteristics of the enrolled patients are listed in Table 1. All the patients enrolled in the standard dosing schedule were female, most were white (80.6%), their mean age was 61.3 years, and most (89.6%) had an ECOG PS of 0. Approximately equal percentages had stage I (47.8%) or stage II disease (52.2%), all had ER-positive disease, and most (74.6%) had progesterone receptor-positive breast cancer. The mean interval from breast cancer diagnosis and surgery to study treatment was 76.3 days and 45.4 days, respectively. All 10 patients receiving the weekly dosing schedule were female, with a mean age of 62.3 years, ECOG PS of 0, and stage I (50.0%) and stage II (50.0%) disease. All had ER-positive disease, and 90.0% had progesterone receptor-positive breast cancer. The mean interval from breast cancer diagnosis and surgery to study treatment was 70.6 days and 47.2 days, respectively.

Feasibility of Eribulin/Capecitabine Combination

Standard Dosing Schedule. A total of 64 patients treated with the standard dosing schedule were evaluable for the primary endpoint. The mean ± standard deviation (SD) RDI was 90.6% ± 11.94% for these patients, and the feasibility rate was 81.3% (95% lower CI limit, 71.4%; $P = .030$, rejecting H_0: feasibility rate ≤ 0.7; Table 2). The RDI and feasibility rates were greater for eribulin (93.5% and 82.8%, respectively) than for capecitabine (87.8% and 71.9%, respectively). This was because more patients required dose reductions and had missed doses of capecitabine than eribulin (Table 2). The AEs considered related to treatment by the investigator and that had led to dose reductions and drug withdrawals are listed in Tables 3 and 4, respectively. Most dose reductions were because of hand-foot syndrome related to capecitabine.

A sensitivity analysis, excluding 9 patients who had undergone dose reductions in violation of protocol (all had experienced ≥ 1 AEs, including grade 1 hand-foot syndrome, elevated aspartate aminotransferase [AST], elevated alanine aminotransferase, fatigue, mouth infection; grade 2 gastritis, mucositis, elevated bilirubin, neuropathy, hyponatremia, and acute renal failure; and grade 3 elevated AST) yielded a feasibility rate of 89.1% (95% lower CI limit, 79.6%; $P = .001$, rejecting H_0: feasibility rate $\leq$ 0.7), with an mean ± SD RDI of 92.9% ± 9.8%. In these 55 patients, the RDI and feasibility rates were somewhat greater for both eribulin (95.1% ± 10.8% and 87.3% ± 77.4%, respectively) and capecitabine (90.6% ± 12.7% and 78.2% ± 67.1%, respectively) than in the evaluable patient data set described above.

The mean ± SD RDI for the 12 patients who received filgrastim was 85.3% ± 15.7% and was 91.9% ± 10.7% for the patients who did not receive growth factors (n = 52). The corresponding overall feasibility rates were 66.7% (95% lower CI limit, 39.1%; $P > .5$, accepting H_0: feasibility rate, ≤ 0.7) and 84.6% (95% lower CI limit, 73.9%; $P = .012$), with no statistically significant difference between the 2 groups ($P = .1510$; Pearson χ^2 test).

Weekly Dosing Schedule. For the 9 evaluable patients who received the weekly capecitabine dosing schedule, the RDI was 95.6% and the feasibility rate was 100% (95% lower CI limit, 71.7%). The RDI and feasibility rates were similar for eribulin (96.6% and 88.9%) and capecitabine (94.6% and 88.9%; Table 2). No patient receiving the weekly dosing schedule had either drug withdrawn because of an AE, and none had missed doses of eribulin, although 6 patients (60.0%) had missed doses of capecitabine (Table 2). Three patients required a reduction in the capecitabine dose because of hand-foot syndrome, rash, or urticaria, and 1 patient required an eribulin dose reduction because of neutropenia. The AEs considered related to treatment and that led to dose reductions are listed in Table 5. Most dose reductions resulted from hand-foot syndrome related to capecitabine.

Table 1 Patient Demographics and Other Baseline Characteristics

Characteristic	Eribulin/Capecitabine	
	Standard Schedule[a] (n = 67)	Weekly Schedule[b] (n = 10)
Age (years)		
Median	62	61
Range	28-80	63-75
Female gender	67 (100)	10 (100)
Race		
White	54 (81)	7 (70)
Black or African American	8 (12)	1 (10)
Native American or Alaskan Native	1 (2)	0 (0)
Hispanic or Latina	4 (6)	2 (20)
Mean BSA (m^2)	1.84 ± 0.207	1.75 ± 0.149
Stage at diagnosis		
I	32 (48)	5 (50)
II	35 (52)	5 (50)
ER positive	67 (100)	10 (100)
Progesterone receptor positive	50 (75)	9 (90)

Data presented as n (%) or mean ± standard deviation, unless otherwise noted.
Abbreviations: BSA = body surface area; ER = estrogen receptor.
[a]Eribulin mesylate 1.4 mg/m^2 on days 1 and 8 plus capecitabine 900 mg/m2 twice daily on days 1 through 14 on a 21-day cycle.
[b]Eribulin mesylate 1.4 mg/m^2 on days 1 and 8 on a 21-day cycle plus capecitabine 1500 mg twice daily on a 7-days on/7-days off schedule for 4 cycles.

Safety/Tolerability

Safety data were available for all patients. Among the patients receiving the standard dosing schedule, 14 (20.9%) experienced treatment-emergent serious AEs (SAEs), with pulmonary embolism in 3 patients (4.5%) and diarrhea in 2 (3.0%). One patient receiving the weekly dosing schedule had a treatment-emergent SAE (worsening anxiety). No treatment-related deaths occurred. Twelve patients (17.9%) required inpatient hospitalization or prolongation of existing hospitalization because of treatment-emergent treatment-related AEs. The reasons for hospitalization included febrile

Table 2 Feasibility and Relative Dose Intensity

Parameter	Patients (n)	Eribulin Plus Capecitabine	Eribulin	Capecitabine
Standard dosing schedule[a]				
Overall feasibility rate (%)	64	81.3	82.8	71.9
95% CI		71.4-100.0	73.2-100.0	61.2-100.0
P value[b]		.030	.015	.431
RDI (%)	64	90.6 ± 11.94	93.5 ± 12.10	87.8 ± 15.40
Dose reductions	67	—	14 (21)	24 (36)
Missed doses	67	—	5 (8)	57 (85)
Drug withdrawal for AEs	67	7 (10.4)	1 (1.5)	5 (7.5)
Weekly dosing schedule[c]				
Overall feasibility rate (%)	9	100.0	88.9	88.9
95% CI		71.7-100.0	57.1-99.4	57.1-99.4
RDI (%)	9	95.6 ± 4.91	96.6 ± 7.64	94.6 ± 5.47
Dose reductions	10	NA	1 (10)	3 (30)
Missed doses	10	NA	0 (0)	6 (60)
Drug withdrawal for AEs	10	NA	0 (0)	0 (0)

Data presented as mean ± standard deviation or n (%), unless otherwise noted.
A total of 12 patients in the standard dosing schedule group and 1 patient in the weekly dosing schedule group received filgrastim.
Abbreviations: AEs = adverse events; CI = confidence interval; NA = not applicable; RDI = relative dose intensity.
[a]Eribulin mesylate 1.4 mg/m^2 on days 1 and 8 plus capecitabine 900 mg/m^2 twice daily on days 1 through 14 on a 21-day cycle.
[b]Observed study feasibility rate compared with 70% using a 1-sample binomial test.
[c]Eribulin mesylate 1.4 mg/m^2 on days 1 and 8 on a 21-day cycle plus capecitabine 1500 mg twice daily on a 7-days on/7-days off schedule for 4 cycles.

neutropenia, pulmonary embolism/deep venous thrombosis, acute renal failure, and chemotherapy-related gastrointestinal disorders.

All patients receiving the standard dosing schedule and the weekly schedule experienced treatment-emergent AEs, most commonly alopecia (77.6% and 90.0%, respectively), fatigue (58.2% and 60.0%,

Table 3 Eribulin- or Capecitabine-Related Adverse Events Leading to Dose Reduction in the Standard Dosing Cohort[a] Stratified by Severity[b]

Adverse Event	All Grades (n = 67)	Grade 2 (n = 67)	Grade 3 (n = 67)	Grade 4 (n = 67)
Hand-foot syndrome	14 (20.9)	5 (7.5)	8 (11.9)	0
Neutropenia	5 (7.5)	0	2 (3.0)	3 (4.5)
Neuropathy, peripheral	5 (7.5)	2 (3.0)	3 (4.5)	0
ALT increase	4 (6.0)	1 (1.5)	0	0
AST increase	3 (4.5)	1 (1.5)	2 (3.0)	0
Fatigue	3 (4.5)	2 (3.0)	1 (1.5)	0
Diarrhea	2 (3.0)	0	2 (3.0)	0
Acute renal failure	1 (1.5)	0	1 (1.5)	0
ALP increase	1 (1.5)	1 (1.5)	0	0
Bilirubin increase	1 (1.5)	1 (1.5)	0	0
Blister	1 (1.5)	0	0	0
Febrile neutropenia	1 (1.5)	0	1 (1.5)	0
Gastritis	1 (1.5)	1 (1.5)	0	0
Hypokalemia	1 (1.5)	0	0	1 (1.5)
Hyponatremia	1 (1.5)	1 (1.5)	0	0
Mucosal inflammation	1 (1.5)	0	1 (1.5)	0
Nausea	1 (1.5)	1 (1.5)	0	0
Oral infection	1 (1.5)	0	0	0
Stomatitis	1 (1.5)	0	1 (1.5)	0
Visual impairment	1 (1.5)	1 (1.5)	0	0

Data presented as n (%).
Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase.
[a]Eribulin mesylate 1.4 mg/m^2 on days 1 and 8 plus capecitabine 900 mg/m^2 twice daily on days 1 through 14 on a 21-day cycle.
[b]No grade 5 adverse events developed.

Table 4 Treatment-Related Adverse Events Leading to Drug Withdrawal in the Standard Dosing Cohort[a]

Adverse Event	Eribulin Only (n = 67)	Capecitabine Only (n = 67)	Eribulin and Capecitabine (n = 67)
Hand-foot syndrome	0	4 (6.0)	1 (1.5)
Neutropenia	0	0	2 (3.0)
Enteritis	0	0	1 (1.5)
Gastritis	0	0	1 (1.5)
Mucosal inflammation	0	1 (1.5)	0
Muscular weakness	1 (1.5)	0	0
Peripheral sensory neuropathy	0	0	1 (1.5)
Pulmonary embolism	0	0	1 (1.5)

Data presented as n (%).
[a]Eribulin mesylate 1.4 mg/m^2 on days 1 and 8 plus capecitabine 900 mg/m^2 twice daily on days 1 through 14 on a 21-day cycle.

respectively), and nausea (52.2% and 40.0%, respectively). A total of 24 patients (35.8%) receiving the standard dosing schedule and 2 (20.0%) receiving the weekly dosing schedule experienced neutropenia (grade 3 or 4 in 21 patients [31.3%] in the standard dosing schedule group and grade 3 in 2 patients [20.0%] in the weekly dosing schedule group). One half of the patients in both cohorts received filgrastim during ≥ 1 cycle of therapy, and 50% received filgrastim during cycles 2, 3, and 4. Also, 27 patients (40.3%) in the standard dosing schedule group and 2 (20.0%) in the weekly dosing schedule group experienced any grade of hand-foot syndrome. One patient receiving the standard dosing schedule had a prolonged QTc interval on the end of study ECG that was not present at baseline.

Discussion

The present study was conducted to assess the feasibility of administering combined eribulin plus capecitabine as adjuvant therapy in postmenopausal patients with early-stage, ER-positive breast cancer. Overall, based on the prespecified criteria that the combination regimen would be considered feasible if ≥ 80% of evaluable patients were able to achieve an RDI of ≥ 85%, the treatment regimen was deemed feasible. Among the patients who received the standard dosing schedule (eribulin mesylate 1.4 mg/m^2 on days 1 and 8 plus capecitabine 900 mg/m^2 twice daily on days 1-14 on a 21-day cycle), the feasibility rate was 81.3% and the RDI was 90.6%. A sensitivity analysis conducted of the patients who underwent treatment dose reductions as recommended per the protocol had a feasibility rate and RDI that were greater at 89.1% and 92.9%, respectively. Furthermore, among the patients who received the weekly dosing schedule (eribulin mesylate 1.4 mg/m^2 on days 1 and 8 of each 21-day cycle plus capecitabine 1500 mg twice daily on a 7-days on/7-days off schedule throughout the 4 cycles), the feasibility rate and RDI were very high at 100% and 95.6%, respectively. These data demonstrate that 4 cycles of eribulin plus capecitabine were generally well tolerated in the adjuvant setting and would support the conduct of a larger trial to evaluate the efficacy of this combination.

The combination of eribulin and capecitabine resulted in AEs that were predictable by their known toxicities. Among the most common AEs in the present study were alopecia, fatigue, nausea, neutropenia, and neuropathy, all known side effects of eribulin.[2,7,8] The most common capecitabine-related AE was hand-foot syndrome. In the present study, most patients were able to achieve and tolerate the full doses of eribulin and capecitabine for 4 treatment cycles receiving the standard dosage schedule and the every-other-week capecitabine schedule. Most dose reductions in the standard schedule group were due to grade 3 hand-foot syndrome attributed to capecitabine (11.9% of patients). Grade 3 hand-foot syndrome has been reported to occur in 8% to 26% of patients receiving capecitabine monotherapy in phase II and III studies of first-line treatment of metastatic breast cancer.[13] Previous studies, for example, have shown grade 3 hand-foot syndrome occurs in 24% of patients with advanced breast cancer treated with a combination of docetaxel and capecitabine[14] and in 11% of patients treated with paclitaxel and capecitabine.[15]

The addition of eribulin did not appear to potentiate capecitabine-related hand-foot syndrome or diarrhea, using either capecitabine dosing schedule. Likewise, capecitabine did not appear to potentiate eribulin-related neuropathy or neutropenia, which was managed in the present study by hematopoietic growth factor support or dose reduction, or both. We recommend the

Table 5 Eribulin- or Capecitabine-Related Adverse Events Leading to Dose Reduction in the Weekly Dosing Cohort[a] Stratified by Severity[b]

Adverse Event	All Grades (n = 10)	Grade 2 (n = 10)	Grade 3 (n = 10)	Grade 4 (n = 10)
Hand-foot syndrome	2 (20)	1 (10)	0	0
Neutropenia	1 (10)	0	1 (10)	0
Rash	1 (10)	0	1 (10)	0
Urticaria	1 (10)	0	0	0

Data presented as n (%).
[a]Eribulin mesylate 1.4 mg/m^2 on days 1 and 8 on a 21-day cycle plus capecitabine 1500 mg twice daily on a 7-days on/7-days off schedule for 4 cycles.
[b]No grade 5 adverse events developed.

every-other-week capecitabine dosing schedule combined with eribulin for further evaluation in the neoadjuvant or adjuvant setting because fewer patients required dose interruptions and/or dose reductions of eribulin or capecitabine. All patients receiving the weekly capecitabine schedule achieved an RDI of $\geq$ 85% compared with 71.9% of patients receiving the standard capecitabine schedule.

Conclusion

The administration of the combination of eribulin plus capecitabine is feasible in postmenopausal patients with early-stage, HER2-negative, ER-positive breast cancer. The addition of eribulin did not appear to increase the expected incidence of capecitabine-related hand-foot syndrome nor did capecitabine appear to exacerbate eribulin-induced neuropathy or neutropenia. Given the effectiveness of combined eribulin plus capecitabine in metastatic breast cancer patients and the safety of this combination, eribulin plus capecitabine is worthy of additional evaluation in the neoadjuvant and/or adjuvant setting in ER-positive early-stage breast cancer patients.

Clinical Practice Points

- Cumulative and overlapping toxicities can limit the therapeutic utility of current drug combinations for adjuvant treatment of ER-positive breast cancer.
- Eribulin and capecitabine have key toxicities that do not overlap; thus, theoretically, eribulin combined with capecitabine should improve the probability that the regimen will be well tolerated.
- From our results, eribulin plus capecitabine as adjuvant treatment is feasible in postmenopausal patients with early-stage, HER2-negative, ER-positive breast cancer.
- The addition of eribulin did not appear to increase the expected incidence of capecitabine-related hand-foot syndrome nor did capecitabine appear to exacerbate eribulin-induced neuropathy or neutropenia.
- The most common AEs observed were alopecia and fatigue.

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Disclosure

J. O'Shaughnessy is a consultant to Eisai Inc. E. Berrak and J. X. Song are employees of Eisai Inc. The remaining authors declare that they have no competing interests.

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